961. *Synthesis of* ^{14}C-*Labelled* 1,4-*Diphenylbutane.*

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The preparation of 1,4-diphenylbutane by two routes is described, one of which is suitable for the small-scale production of ^{14}C-labelled material.

Other routes for the production of this type of compound have been investigated.

The conditions for successful condensations involving alkyl-lithiums and Grignard reagents, and possible reaction mechanisms, are discussed.

In a programme concerning the metabolism of various types of hydrocarbons and related silicon compounds, a synthetic method for the production of small amounts of ^{14}C-labelled 1,4-diphenylbutane of very high specific activity was required. 1,4-Diphenylbutane has been obtained mostly as a by-product in poor yield or has been prepared by reactions unsuitable for small-scale production of a labelled compound.[1] We thus tried a series of newer methods.

(1) Condensing benzyl bromide with labelled ethyl malonate gave β-phenyl[α-^{14}C]-propionic acid, $\mathrm{Ph{\cdot}CH_2Br + {}^*CH_2(CO_2Et)_2 \longrightarrow Ph{\cdot}CH_2{\cdot}{}^*CH_2{\cdot}CO_2H}$, but electrolysis of

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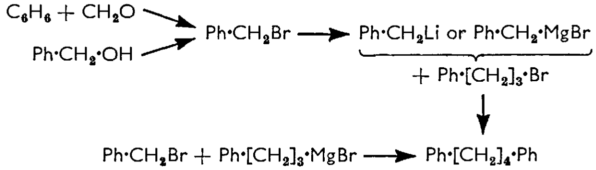
[1] Fichter and Senti, *Zeitscrift Alexander Tschirsh*, 1926, 410; *Sep. Basel, Anst. für anorg. Chem.*, *Chem. Zentr.*, 1927, II, 54; Eventova and Christyakova, *Vestnik Moskov. Univ.* (*Ser. Fiz.-Mat*)., 1954, **9**, No. 3, 91; *Chem. Abs.*, 1955, **49**, 8890; Reppe, *Annalen*, 1955, **596**, 1; Cram and Steinberg, *J. Amer. Chem. Soc.*, 1951, **73**, 5691; Boelhonwer and Waterman, *Research*, 1956, No. 3, S11.

sodium β-phenylpropionate gave on the platinum anode a brittle coating of a brown substance with a high softening point. This was presumably a polymer arising from phenethyl radicals and the method was abandoned.

(2) Avoiding the use of phenethyl derivatives we then condensed benzoyl chloride with bis-3-phenylpropylcadmium, and γ-phenylbutyryl chloride with diphenylcadmium,[2] labelling being in both cases on the carbonyl group. Both reactions gave γ-phenyl-[α-^{14}C]butyrophenone, which was reduced by the Wolff–Kishner method to 1,4-diphenyl-[α-^{14}C]butane, $Ph\cdot{}^{*}CH_2\cdot[CH_2]_3\cdot Ph$. These methods, although successful, involved several stages, and yielded only 30% of pure product (calculated on the barium carbonate used) and allowed labelling in only one position.

(3) The following methods appear to have the advantage of allowing labelling in the benzene rings or the carbon chain or both and to involve the radioactive atom in fewer stages:



Organolithium derivatives have been used by Paul and Pover[3] in similar condensations for the preparation of silicon-containing analogues of paraffins.

Syntheses of these Grignard reagents and organolithium derivatives were successful in diethyl ether; but the latter could not be prepared in butyl ether, pentane, hexane, or dioxan; and the Grignard reagents could be prepared in butyl ether but not in dioxan or tetrahydrofuran.

The condensations, however, did not give the required product, except in one instance from 3-phenylpropylmagnesium bromide and benzyl bromide, a reaction that could not be repeated. Altering reaction conditions such as temperature, time of heating, and solvent was unsuccessful.

(4) The Grignard reagent from 1,4-dibromobutane was prepared in ether but attempted condensation with bromobenzene led only to recovery of the starting materials. An attempt to condense phenylmagnesium bromide with 1,4-dibromobutane in ether was also unsuccessful, as was condensation between tetramethylenedimagnesium bromide and bromobenzene. Eventova and Chistyakova[1] obtained only a poor yield in attempting the self-condensation of phenethyl bromide in the presence of sodium; we therefore varied this method by condensing bromobenzene with dibromobutane. As ring-labelled bromobenzene is readily available, such a reaction has the advantage, not only of involving a single stage, but also of allowing labelling in both benzene rings, with an increase in specific activity. This reaction, in ether, in the presence of sodium, gave 1,4-di[*o*-^{14}C]phenylbutane of high specific activity in 75% yield. The method is particularly adaptable to small-scale handling in modified Stang reactors and can be carried out without the use of high-vacuum techniques on a 100-mg. scale.

EXPERIMENTAL

Radiochemicals were supplied by the Radiochemical Centre, Amersham, phenylalkyl compounds were purchased from Eastmann-Kodak Ltd., and other materials were either of " Laboratory Reagent " or " AnalaR " grade. γ-Phenyl[α-^{14}C]butyric acid was prepared by carbonation with $^{14}CO_2$ of the Grignard reagent of 3-phenylpropyl bromide by Lemmon's method quoted by Calvin *et al.*[4]

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[2] Cf. Cason and Prout, *J. Amer. Chem. Soc.*, 1944, **66**, 46; 1946, **68**, 2078.

[3] Paul and Pover, *Arch. Biochem. Biophys.*, 1960, **87**, 312.

[4] Calvin, Heidelberger, Reid, Tolbert, and Yankwick, " Isotopic Carbon," Chapman and Hall, London, 1949, p. 178.

γ-Phenylbutyryl Chloride.—γ-Phenylbutyric acid (20 g.) was refluxed with an excess of redistilled thionyl chloride for 3 hr., affording the acid chloride (21·5 g.), b. p. 137°/11 mm. It was stored at 5°.

Diphenylcadmium.—To the Grignard reagent from bromobenzene (10 g.), magnesium (1·8 g.), and ether (40 ml.), at 0°, anhydrous cadmium chloride (6·5 g.) was added with stirring during 5 min. The suspension was refluxed and stirred until it gave a negative Gilman test (25 min.).[5] Ether was then distilled from the mixture until distillation was slow. Dry benzene (25 ml.) was added, and a further 10 ml. of distillate were collected. A further 40 ml. of dry benzene were added.

γ-Phenylbutyrophenone.—To a hot, stirred solution of diphenylcadmium γ-phenylbutyryl chloride (6·1 g.) in benzene (10 ml.) was added. After the vigorous exothermic reaction the mixture was stirred under reflux for a further 10 min. The precipitate was poured on ice and sulphuric acid, which was then extracted with benzene (2 × 30 ml.). The extract was washed with water, 5% sodium carbonate solution, water, and saturated sodium chloride solution, dried (Na_2SO_4), filtered, and evaporated, to give 6·5 g. (85%) of γ-phenylbutyrophenone. Recrystallisation from methanol gave 4·6 g. of the pure product, m. p. 52° (Found: C, 85·6; H, 7·4. Calc. for $C_{16}H_{16}O$: C, 85·7; H, 7·2%) (2,4-dinitrophenylhydrazone, m. p. 133—134°).

Synthesis of 1,4-Diphenylbutane by Reduction of γ-Phenylbutyrophenone.—γ-Phenylbutyrophenone (2 g.) was dissolved in triethylene glycol (5 ml.) and added to hydrazine hydrate (1 g.) and sodium hydroxide (500 mg.) dissolved in the minimum of water. The mixture was heated at 120° for 3 hr., then at 200° for a further 2 hr. After cooling, water (20 ml.) was added, and the solution extracted with light petroleum (2 × 10 ml.). The extract was evaporated and the residue recrystallised from methanol, to give 1,4-diphenylbutane, needles (1·53 g., 83%), m. p. 53—54° (Found: C, 91·3; H, 8·5. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%).

Preparation of Organolithium Derivatives.—Lithium (2 g., 1·4 mol.) in thin strips was added to sodium-dried ether (50 ml.), followed quickly by benzyl chloride (11·5 ml., 1 mol.) in ether (15 ml.). The mixture was stirred at room temperature for 6 hr. and then overnight with refluxing. A cloudy yellow solution was formed, with a little unchanged metal and much white solid. Removal of the precipitate and metal yielded a clear solution of benzyl-lithium.

3-Phenylpropyl-lithium was similarly prepared from 3-phenylpropyl bromide.

Preparation of Grignard Reagents.—These were obtained from 3-phenylpropyl bromide, benzyl bromide, and 1,4-dibromobutane with magnesium activated by iodine in ether.

Reaction of 3-Phenylpropylmagnesium Bromide with Benzyl Bromide.—Condensation of 1 mol., each of the reactants in ether under reflux overnight, and then treatment with water and 5% sulphuric acid at 0°, gave 1,4-diphenylbutane (25%) as needles, m. p. 51—52°, in one experiment only.

Preparation of 1,4-Diphenylbutane.—To finely divided sodium ($\sim$0·25 g.) in sodium-dried ether (2·5 ml.) was added quickly a mixture of 1,4-dibromobutane (185 mg.), carrier bromobenzene (260 mg.), and bromo[^{14}C]benzene (8·3 mg., 0·1 mc) in ether (1·5 ml.). The mixture was then refluxed with nitrogen bubbling through the solution for 3 hr., during which an intense blue colour developed and precipitation occurred. The excess of sodium and the precipitated sodium bromide were removed through a sintered-glass filter, and the ether was evaporated. The residue recrystallised from methanol, yielding 1,4-diphenylbutane (135 mg., 75%), m. p. 51—52° (Found: C, 91·2; H, 8·6. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%), $\nu_{\text{max.}}$ 3000s, 1600m, 1490s, 1950s, 1025m, 749vs, 698vs cm.$^{-1}$.

Derivatives. 1,4-Diphenylbutane (0·2 g.) and nitric acid (*d* 1·5; 2 ml.), mixed at 0°, left at room temperature for 30 min., and then poured into water (5 ml.), gave a precipitate which was boiled with alcohol and recrystallised first from acetic acid and then from pyridine, yielding pale yellow needles of 1,4-bis-2,4-dinitrophenylbutane (54%), m. p. 204—205° (cf. ref. 6).

1,4-Diphenylbutane (2·1 g.), *N*-bromosuccinimide (3·6 g.), and benzoyl peroxide (50 mg.) in carbon tetrachloride (50 ml.) were refluxed for 30 min., then filtered and evaporated. The residue of 1,4-dibromo-1,4-diphenylbutane recrystallised from ethanol as needles (70%), m. p. 119—120° (cf. ref. 7).

The dibromo-compound (1·2 g.) was refluxed in dry pyridine for 45 min. On cooling, colourless crystals separated. The pyridine was removed under reduced pressure and the

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[5] Gilman and Schulze, *J. Amer. Chem. Soc.*, 1925, **47**, 2002.

[6] Fichter and Stenzel, *Helv. Chim. Acta*, 1939, **22**, 970.

[7] Israelashvili and Bergmann, *J.*, 1953, 1070.

residue steam-distilled. White plates which appeared in the distillate were recrystallised from alcohol, to yield 1,4-diphenylbutadiene (47%), m. p. 151—152°.

DISCUSSION

The present study confirms the findings of other workers, including Kameoka's failure[8] with 1,4-dibromobutane in diethyl ether, to the effect that condensation of Grignard reagents with halogenoalkanes is not in general suitable for the preparation of products with longer chains. Kawai and Tsutsumi[9] obtained hexa-1,5-diene from allyl bromide and allyl-lithium in diethyl ether, and here it is noteworthy that both compounds contain the same carbon chain and that double-bond isomerism of the allyl radical regenerates itself, these two factors preventing formation of alternative condensation products.

If the Wurtz–Fittig reaction is assumed to involve formation of a species R^-Na^+, the successful synthesis of butylbenzene from bromobenzene, butyl bromide, and sodium can be assumed to depend on easier reaction of butyl bromide than of bromobenzene with phenylsodium; a similar assumption can be applied to our success with 1,4-dibromobutane. If the Wurtz–Fittig reaction is assumed to involve free radicals, then we need to assume that the tetramethylene diradical or the 4-bromobutyl radical is more reactive than the phenyl radical. Such an assumption is in line with results reported by Vogel[10] for bromobenzene and butyl bromide.

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[8] Kameoka, *J. Chem. Soc. Japan*, 1960, **81**, 268.
[9] Kawai and Tsutsumi. *J. Chem. Soc. Japan*, 1960, **81**, 109.
[10] Vogel, " Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p. 508.